

AMENDMENT TO THE CLAIMS:

This listing of Claims will replace all prior versions of Claims in the application.

Listing of Claims:

1-88. (Canceled)

89. (New) A composition comprising a modified animal cell or a progeny thereof, said modified animal cell comprising at least one modification sequence, said composition being produced by a method comprising introducing a targeting DNA construct into a plurality of cells of an inbred strain of animal in vitro, wherein said targeting DNA construct comprises a targeting DNA sequence that is capable of homologous recombination with a non-selectable target DNA sequence in the genome of said plurality of cells, and wherein said targeting DNA sequence comprises: (i) said at least one modification sequence, and (ii) flanking sequences that are derived from said inbred strain of animal.

90. (New) The composition of claim 89, said method further comprises incubating said plurality of cells under conditions where said targeting DNA sequence undergoes homologous recombination with said target DNA sequence in the genome of said plurality of cells.

91. (New) The composition of claim 90, wherein said targeting DNA construct is produced in a prokaryotic cell.

92. (New) The composition of claim 91, wherein said prokaryote is *E. coli*.

93. (New) The composition of claim 90 wherein 5% to 25% of said plurality of cells have undergone homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence.

94. (New) The composition of claim 90 wherein 10% to 90% of said plurality of cells have undergone homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence.

95. (New) The composition of claim 90 wherein 30% to 50% of said plurality of cells have undergone homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence.

96. (New) The composition of claim 89 or 90, wherein said inbred strain of animal is a non-murine animal, a non-human animal, a mammal, or a vertebrate.

97. (New) The composition of claim 89 or 90, wherein said inbred strain of animal is a mouse.

98. (New) The composition of claim 89 or 90, wherein said modified animal cell is a stem cell, a germ cell, or a somatic cell.
99. (New) The composition of claim 89 or 90, wherein said modified animal cell is a hematopoietic cell, a T-lymphocyte, an epithelial cell, an endothelial cell, an adrenal medulla cell, a keratinocyte, a fibroblast, an osteoblasts, an osteoclasts, a neuron, a ganglion cell, a retinal cell, a liver cell, a myoblast cell, or a cell of the Islets of Langerhans.
100. (New) The composition of claim 89 or 90, wherein said modified animal cell is an embryonic stem cell.
101. (New) The composition of claim 89 or 90, wherein said target DNA sequence comprises a coding region, a promoter, an enhancer, a terminator, an intron, or an inter-genic region.
102. (New) The composition of claim 89 or 90, wherein each of said flanking sequences is at least about 75, 100, 150, 200, 300, 500, 1,000, 2,500, 8,000 or 15,000 base pairs.
103. (New) The composition of claim 89 or 90, wherein each of said flanking sequences is at least 97%, 99%, 99.5%, 99.6%, or 99.9% identical to said target DNA sequence.
104. (New) The composition of claim 89 or 90, wherein said target DNA sequence and each of said flanking sequences comprises at least about 75, 150, or 500 base pairs in length that are 100% identical.
105. (New) The composition of claim 89 or 90, wherein said targeting DNA sequence is derived from cells of the same individual animal or a sibling thereof, as cells comprising said target DNA sequence.
106. (New) The composition of claim 89 or 90, wherein said targeting DNA construct comprises a gene that is a selectable marker, an antibiotic resistance gene, a gene conferring the ability to grow on selected substrates, or a gene encoding proteins that produce detectable signals.
107. (New) The composition of claim 106, wherein said gene is positioned in an intron in the targeting DNA.
108. (New) The composition of claim 106 wherein said gene comprises a transcriptional start signal, a translational start signal, and/or a termination signal.
109. (New) The composition of claim 106 wherein said gene is a neomycin resistance gene, a hygromycin resistance gene, a thymidine kinase gene, a hypoxanthine phosphoribosyl transferase gene, or a guanine/xanthine phosphoribosyl transferase gene.
110. (New) The composition of claim 108, wherein said transcriptional start signal comprises a metallothionein promoter, a thymidine kinase promoter, a beta-actin promoter, an immunoglobulin promoter, a SV40 promoter, or a human cytomegalovirus promoter.
111. (New) The composition of claim 89 or 90, wherein said modification sequence comprises a gene that is a selectable marker, an antibiotic resistance gene, a gene conferring

the ability to grow on selected substrates, or a gene encoding proteins that produce detectable signals.

112. (New) The composition of claim 89, wherein said introducing step comprises the use of microinjection, electroporation, transfection, calcium phosphate precipitation, liposomes, viral capsids, protoplast fusion, or ballistic penetration.

113. (New) The composition of claim 90, wherein said method further comprises selecting said plurality of cells.

114. (New) The composition of claim 90, wherein said target DNA sequence in said modified animal cell is modified by an insertion, a deletion, a substitution, or a combination thereof.

115. (New) The composition of claim 89 or 90, wherein said at least one modification sequence is a sequence that is not present in the genome of said inbred strain of animal.

116. (New) The composition of claim 114, wherein said deletion comprises a deletion of at least one exon, at least one intron, at least a non-coding region, or a combination thereof.

117. (New) The composition of claim 90, wherein said at least one modification sequence disrupts or enhances expression of a coding sequence in said target DNA sequence.

118. (New) The composition of claim 90, wherein said homologous recombination comprises a single crossover, a double crossover, or a gene conversion.

119. (New) The composition of claim 90, wherein an allele of a gene in said target DNA has been modified.

120. (New) The composition of claim 119, wherein the other allele of said gene has been modified.

121. (New) The composition of claim 89 or 90, wherein said inbred strain of animal is 129 strain of mouse or BALB/c strain of mouse.

122. (New) The composition of claim 89 or 90, wherein said plurality of cells are cells of a substrain of said inbred strain of animal.

123. (New) The composition of claim 89 or 90, wherein said targeting DNA sequence is from a substrain of said inbred strain of animal.

124. (New) The composition of claim 89 or 90, wherein said plurality of cells are derived from a first substrain of said inbred strain of animal and said targeting DNA sequence is from a second substrain of said inbred strain of animal.

125. (New) The composition of claim 124 wherein said first substrain and said second substrain are the same substrain.

126. (New) The composition of claim 89 or 90, wherein said at least one modification sequence comprises a nucleic acid that encodes a polypeptide and wherein said modified animal cell produces said polypeptide.

127. (New) The composition of claim 90, wherein said at least one modification sequence corrects a defective gene in said target DNA.